

**REMARKS/ARGUMENTS**

**Status of the claims**

Claims 1-41 are pending and under examination. Claims 1-15 and 20-41 are rejected. Claims 16-19 are indicated as allowable if rewritten in independent form.

Claims 1 and 27 were amended to reflect proper subscript notations. These amendments add no new matter.

**Rejection under 35 U.S.C. § 102(b)**

The Action rejects claims 1, 22-26, and 28-34 as allegedly anticipated by *Caruthers et al.* (U.S. Patent No. 5,750,666). Applicants respectfully traverse.

For a rejection under § 102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that there can be no difference between an anticipatory reference and the claimed subject matter:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the claimed invention.

The Caruthers reference, however, does not disclose every element of the presently claimed invention. For example, the Caruthers reference neither expressly nor inherently discloses a method of synthesizing an oligomer wherein an extended compound is treated in a single step with a mixture comprising both an oxidizing reagent and a capping reagent. Although the Action directs Applicants' attention to Caruthers' Example XX in an attempt to establish anticipation, Example XX neither teaches nor suggests the claimed methods. Instead, the example presents what had been the common wisdom in the art of polynucleotide synthesis, *i.e.*, that the capping reagent and oxidizing reagent must be added to the extended oligomeric compound in separate steps. According to Caruthers, there are four major steps in polynucleotide synthesis. The patent, for example, identifies the capping and oxidation steps as independent steps 3 and 4 (column 52, lines 53-62), and teaches that between these steps additional washing steps are required to remove unwanted solvents and reagents (column 52, lines 62-65). There is no suggestion in the Caruthers patent that a growing oligomer can or should be treated with both an oxidizing reagent and a capping reagent in a single step.

The Action mistakenly suggests otherwise in directing Applicants' attention to col. 53, lines 21-30 of the Caruthers patent, which describes a method for synthesizing phosphorodithioate linkages. In this method, however, Caruthers similarly fails to teach that an extended oligomeric compound can be treated with an oxidizing reagent and a capping reagent in a single step. In fact, even the Action acknowledges that this section of the Caruthers patent does not even mention a capping step. Since the patent does not mention a capping step or any capping reagent, and since a capping reagent is expressly recited in Applicants' claims, this cited disclosure from the Caruthers patent falls far short of anticipating the methods of the present invention. Accordingly, Applicants respectfully

request that the rejection of claims 1, 22-26, and 28-34 under 35 U.S.C. §102(b) be withdrawn.

**First rejection under 35 U.S.C. § 103**

The Action rejects claims 1-8, 12-14, 20-21, 31, 33-34, and 39-41 under 35 U.S.C. § 103(a) as allegedly unpatentable over Hirschbein (U.S. Patent No. 5,166,387) in view of Agrawal (U.S. Patent No. 5,149,798). Applicants request reconsideration because there is no evidence indicating that those of ordinary skill would have been motivated to combine the cited teachings of the Hirschbein and Agrawal patents, and because such combination – even if motivated – would not have produced any claimed invention.

As explained in the MPEP, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their respective teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Office Action, however, fails to identify any motivation or suggestion in the cited references to modify their respective teachings, much less to treat an extended oligomeric compound with an oxidizing reagent and capping reagent in a single step. Furthermore, there is no evidence of record suggesting the desirability or even possibility of such a combination. As noted on page 5 of the Action, the Hirschbein reference neither teaches nor suggests such

a method. In fact, what the Hirschbein patent teaches is that oxidation and capping should be performed in separate steps. Although the Action attempts to rely on the teachings of the Agrawal patent to remedy this telling deficiency, the Action fails to identify anything in the Agrawal patent that teaches or suggests the methods of the present invention. In fact, the Agrawal patent teaches away from the present invention. Agrawal teaches a process for synthesizing oligonucleotides, wherein the **capping and coupling** steps rather than the capping and oxidation steps are combined. For Example, see column 3, lines 61-64 of the Agrawal patent where it is stated that "failed sequences are capped by excess activation reagent in the **coupling step**, thereby obviating the need for a separate capping step and reagent"(emphasis added).

It is also unclear how a person of ordinary skill who did not have benefit of the hindsight provided by Applicants' disclosure would have attempted to combine the teachings of the Hirschbein and Agrawal patents, much less that such a person would have combined the references' teachings in a way that would have produced a claimed invention. The Hirschbein patent discloses a synthesis method having separate coupling, oxidation and capping steps, whereas the Agrawal patent discloses a synthesis method having a combined coupling and capping step and a separate oxidation step. There is nothing in the prior art of record suggesting how these divergent teachings should be reconciled or, for that matter, that they can be reconciled. In stark contrast to both the Hirschbein and Agrawal methods, the present claims are directed to synthesis methods comprising a combined oxidation and capping step. Since there is nothing suggesting that a combination of the cited references would have produced a claimed invention, Applicants respectfully request that the rejection for alleged obviousness be reconsidered and withdrawn. *In re Payne*, 203 U.S.P.Q. 245, 255

(C.C.P.A. 1979)(references relied upon to support rejection under § 103 must place the claimed invention in the possession of the public).

**Additional rejections under 35 U.S.C. § 103**

The Action rejects claims 1-7, 9-12, 20-21, 23-24, 28-31, and 33-41 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ravikumar (U.S. Patent No. 5,614,621) in view of Agrawal; and claims 37-38 under 35 U.S.C. § 103(a) as allegedly unpatentable over Caruthers 2 in view of Agrawal and Krotz (U.S. Patent No. 6,399,765). Applicants respectfully traverse these rejections, because the Ravikumar and Krotz patents (both of which are assigned to ISIS Pharmaceuticals) are not available as prior art under 35 U.S.C. § 103.

Effective November 29, 1999, subject matter which was prior art under former 35 U.S.C. § 103 via 35 U.S.C. § 102(e) is now disqualified as prior art against the claimed invention if that subject matter and the claimed invention were, at the time the invention was made, . . . subject to an obligation of assignment to the same person.

MPEP § 706.02(k).

Accordingly, the rejections based on these patents are improper and should be withdrawn.

The Action also rejections claims 1-6, 9-11, 15, and 22-34 under 35 U.S.C. § 103(a) as allegedly unpatentable over Caruthers (U.S. Patent No. 4,458,066, "Caruthers 2") in view of Santamaria (U.S. Patent No. 5,424,184) and Agrawal. As noted on page 10 of the Action, the Caruthers 2 patent does not teach treating an extended compound with a mixture comprising an oxidizing and capping reagent in a single step. The Santamaria patent (which is cited for the proposition that an oligomer can be capped with a combination of acetic anhydride and 1-methylimidazole in tetrahydrofuran and pyridine) also does not teach treating an extended compound with a mixture comprising an oxidizing and capping reagent

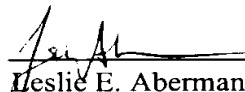
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in a single step. As previously discussed, the Agrawal patent does not supply the missing teaching. Accordingly, the Applicants respectfully request that the rejection of the claims as allegedly unpatentable under § 103(a) be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicant submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested

Date: May 28, 2003

  
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Under 37 CFR 10.9(b) attached

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